Remarks

The Amendments

Claims

Claims 2, 20, 29, 32, and 35 have been amended to recite that the nucleic acid complexes "are formed by mixing said nucleic acid molecule and said polycation molecules, wherein prior to mixing said polycation molecules have a counterion." The amendment is supported by the specification which discloses that nucleic acid complexes are produced when the "nucleic acid is mixed with the polycation having acetate, bicarbonate, or chloride as a counterion." (Page 3, lines 5-7.) Claims 2, 20, 29, 32, and 35 have also been amended to recite that the nucleic acid complexes "are rod-shaped when visualized by transmission microscopy." This amendment is supported by the specification which discloses, "Morphology [of compacted nucleic acids] was visualized by transmission electron microscopy (Fig. 10 and Fig. 17). DNA condensed with acetate and bicarbonate salts of CK30 polylysine assumed forms of long (100-300 nm) and narrow (10-20 nm) rods." (Page 15, lines 3-5.) This amendment is also supported by the specification which discloses that "CK45/chloride (Fig. 17) gave results similar to CK30/acetate." (Page 15, lines 8-9.)

Claims 47-50 have been amended to recite the recitations of method claims 10, 38, 41, and 44 in place of "made by the process of." The method claims were canceled as directed to a non-elected invention. The processes recited in claims 47-50 also recite that the complexes "are rod-shaped when visualized by transmission electron microscopy," which is supported as indicated above.

Claims 5, 25, 71, 76, 81, 108, and 124 have been amended to recite that the "rod-shaped complexes have a length of 100-300 nm when visualized by transmission electron microscopy" in place of the "complex is compacted to a diameter of less than 90 nm [or 50 nm]." New claims 191, 195, 199, and 203 recite nucleic acid complexes that "have a length of 100-300 nm." Claims 7, 27, 73, 78, 83, 110, and 126 have been amended to recite that the "rod-shaped complexes have a diameter of 10-20 nm when visualized by transmission electron microscopy" in place of the "complex is compacted to a diameter less than 23 nm." New claims 193, 197, 201, and 205 recite nucleic acid complexes that "have a length of 10-20 nm." Claims 8, 28, 74, 79, 84, 111, and 127 have been amended to recite that the "rod-shaped complexes have a length of 100-300 nm and a diameter of 10-20 nm when visualized by transmission electron microscopy" in place of the "complex is compacted to a diameter not more than 12 nm." New claims 194, 198, 202, and 206 recite nucleic acid complexes that "have a length of 100+-300 nm and a diameter of 10-20 nm." These amendments are supported by the specification which discloses that "DNA condensed with acetate and bicarbonate salts of CK30 polylysine assumed forms of long (100-300 nm) and narrow (10-20 nm) rods." (Page 15, lines 3-5.)

Claims 6, 26, 72, 77, 82, 109, and 125 have been amended to recite that the "rod-shaped complexes have a length of 100-200 nm when visualized by transmission electron microscopy" in place of the "complex is compacted to a diameter less than 30 nm." New claims 192, 196, 200, and 204 recite nucleic acid complexes that "have a length of 100-200 nm." This amendment is supported by the specification which discloses that compaction with "[a]cetate leads to longer rods of 100 to 200 nm." (Page 13, lines 1-2.)

Claim 20 has been amended to recite "polycation molecules" in place of "polycation molecule." Claims 105, 118, 132, 140, 148, and 177-181 have been amended to recite " the polycation molecules are" in place of " the polycation is." Claims 106, 107, 119, 120, 133, 134, 141, 142, 149, and 150 have been amended to recite "the polycation molecules comprise" in place of "the polycation molecule comprises." These amendments to claims 20, 105-107, 118-120, 132-134, 140-142, 148-150, and 177-181 merely correct antecedent basis for "polycation molecules" in the claims from which they depend and do not narrow the scope of the claims.

New claims 187-190 recite that the nucleic acids in the compositions of claims 2, 20, 32, and 35 "are associated with a lipid." These claims are supported by claim 70, which recites that the nucleic acids in the composition of claim 29 "are associated with a lipid."

New claim 207 recites the method of claim 131, "wherein the composition does not contain a disaccharide." Claim 207 is support by claim 117 which similarly recites that "the composition does not contain a disaccharide."

New claim 208 recites a method of delivering polynucleotide to cells comprising "contacting the composition of claim 139 with cells, whereby the polynucletoide is delivered to and taken up by the cells." Claim 208 is supported by originally filed claim 154 which recites a similar method.

Specification

The specification has been amended at the description of Figures 16 and 18 to incorporate the text that was removed from amended Figures 16 and 18.

The specification has also been amended to correct a grammatical error.

Drawings

Figures 16, 17, 18, 19, and 20 have been amended to remove excess text.

None of the amendments introduces new matter.

The Rejection of Claims 2, 20, 29, 32, and 35 Under 35 U.S.C. § 112, Second Paragraph

Claims 2, 20, 29, 32, and 35 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

The Office Action asserts that the recitation "whichever is larger" in claims 2, 20, 29, 32, and 35 is indefinite because it is unclear to what "whichever" refers. The recitation "whichever is larger" and the elements to which it refers have been deleted from the claims.

Withdrawal of this rejection to claims 2, 20, 29, 32, and 35 is respectfully requested.

The Rejection of Claims 2, 3, 5-7, 9, 20, 21, 23-27, 29, 30, 32-36, 47, 49, 51, 55, 69-73, 75-78, 80-83, 85, 103, 104, and 164 Under 35 U.S.C. § 102(e) or 35 U.S.C. § 103(a)

Claims 2, 3, 5-7, 9, 20, 21, 23-27, 29, 30, 32-36, 47, 49, 51, 55, 70-73, 76-78, 81-83, 103, 104, and 164 have been rejected under 35 U.S.C. § 102(e) as anticipated by or under 35 U.S.C. § 103(a) as unpatentable over Hanson *et al.* (U.S. Patent 5,844,107). Claims 9, 69, 75, 80, 85, 103, 104, and 164 have been canceled. Thus the rejection as it applies to these claims is rendered moot. Applicants respectfully traverse the rejection as it applies to claims 2, 3, 5-7, 20, 21, 23-27, 29, 30, 32-36, 47, 49, 51, 55, 70-73, 76-78, and 81-83.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

To reject a claim as *prima facie* obvious three criteria must be met:

First, there must be some suggestion or motivation, either in

> the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP § 1243.

Claims 2, 20, 29, 32, 35, 47, and 49 are the independent claims of the rejected claim set. Amended claims 2, 20, 29, 32, and 35 are directed to non-naturally occurring nucleic acid complexes. The complexes consist essentially of a single nucleic acid molecule and one or more polycation molecules. The complexes are formed by mixing the nucleic acid molecule and the polycation molecules. Prior to mixing, the polycation molecules have a counterion selected form the group consisting of acetate, bicarbonate, and chloride. The complexes are rod-shaped when visualized by transmission electron microscopy.

Amended claims 47 and 49 are directed to non-naturally occurring, soluble compacted complexes of a nucleic acid and a polycation molecule that are made by a process. The process includes a step of mixing a nucleic acid with a polycation. The polycation has acetate as a counterion. The complexes produced by the process consist essentially of a single nucleic acid molecule and one or more polycation molecules. The complexes are rod-shaped when visualized by transmission electron microscopy.

Hanson teaches complexes of a nucleic acid and a nucleic acid-binding carrier, such as polylysine. The complexes are compacted without aggregation or precipitation. (Column 19, lines 50-52.) The complexes are not, however, "rod-shaped when visualized by transmission electron microscopy" as recited in claims 2, 20, 29, 32, 35, 47, and 49. The complexes taught by Hanson are spherical or toroid-shaped. Hanson teaches, "Condensed DNA is in a state in which interaction with the solvent is minimal and therefore the DNA is

in the form of isolated spheres or toroids." (Column 19, lines 60-62.) Thus Hanson does not expressly or inherently teach DNA complexes that "are rod-shaped when visualized by transmission electron microscopy" as recited in claims 2, 20, 29, 32, 35, 47, or 49. Claims 3, 5-7, 21, 23-27, 30, 33, 34, 36, 51, 55, 70-73, 76-78, and 81-83 depend from these claims and thus also contain this recitation. Hanson does not anticipate claims 2, 3, 5-7, 20, 21, 23-27, 29, 30, 32-36, 47, 49, 51, 55, 70-73, 76-78, and 81-83.

Hanson also does not suggest DNA complexes that "are rod-shaped when visualized by transmission electron microscopy." Hanson teaches that properly condensed DNA is visualized only as spheres or toroids. "Condensed DNA is in a state in which interaction with the solvent is minimal and therefore the DNA is in the form of isolated spheres or toroids." (Column 19, lines 60-62.) In fact, Hanson teaches that properly condensed DNA is in the shape of a toroid. Hanson teaches that if "DNA is **properly** condensed; only individual toroids can be seen." (Column 6, lines 8-9, emphasis added.) Thus, Hanson only suggests DNA complexes that have the shape of a sphere or toroid. Hanson does not suggest nucleic acid complexes that "are rod-shaped when visualized by transmission electron microscopy" as recited in claims 2, 20, 29, 32, 35, 47, or 49. Claims 3, 5-7, 21, 23-27, 30, 33, 34, 36, 51, 55, 70-73, 76-78, and 81-83 depend from these claims and thus also contain this recitation. The *prima facie* case of obviousness must fail. Hanson does not render claims 2, 3, 5-7, 20, 21, 23-27, 29, 30, 32-36, 47, 49, 51, 55, 70-73, 76-78, and 81-83 obvious.

Further, Hanson also does not expressly or inherently teach that the polycation is a polylysine peptide with a cysteine residue as is recited in dependent claim 34 of the rejected claim set. The Office Action acknowledges that Hanson does not provide this teaching:

"Hanson teaches a compacted and spherical condensed polylysine/DNA complex comprising a single nucleic acid . . . wherein the polylysine has not been modified at its N-terminal to incorporate a cysteine residue." (Paper 12, page 4, lines 3-5.) Thus Hanson further cannot expressly or inherently teach each and every element of claim 34. The rejection to claim 34 as anticipated by Hanson should be withdrawn.

Hanson also does not suggest nucleic acid complexes containing a polycation that is a polylysine with a cysteine residue as recited in claim 34. Hanson teaches that the polycation is preferably polylysine. Hanson further teaches that the polycation may contain amino acids other than lysine, but only suggests arginine or ornithine as the other amino acid. Hanson teaches, "A preferred polycation is polylysine. Other potential nucleic acid binding moieties include Arg-Lys mixed polymers, polyarginine, polyornithine, histones, avidin, and protamines." (Column 16, lines 15-18.) Thus Hanson does not suggest that "polycation molecules are polylysine peptides with a cysteine residue" as recited in claim 34. The *prima facie* case of obvious of this claim must fail.

Withdrawal of this rejection to claims 2, 3, 5-7, 9, 20, 21, 23-27, 29, 30, 32-36, 47, 49, 51, 55, 70-73, 76-78, 81-83, and 164 under 35 U.S.C. § 102(e) and/or 35 U.S.C. § 103(a) is respectfully requested.

<u>The Rejection of Claims 2-7, 9, 20-27, 29-37, 47, 49, 51, 52, 55, 56, 69-73, 75-78, 80-83, 85, 103-110, 112-126, 128-159, 164, and 177-181 Under 35 U.S.C. § 103(a)</u>

Claims 2-7, 9, 20-27, 29-37, 47, 49, 51, 52, 55, 56, 69-73, 75-78, 80-83, 85, 103-110, 112-126, 128-159, 164, and 177-181 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Hanson *et al.* (U.S. Patent 5,844,107) taken with Park *et al.* (U.S. Patent 6,177,274), Schacht (WO 98/19710), and in further in view of either Serres *et al.*

(*Langmuir* (1999) *15*:6956-6960) or Lollo (WO 97/30731). Claims 9, 69, 75, 80, 85, 103, 104, 112, 128, 136, 144, 155-159, and 164 have been canceled. Thus the rejection to these claims has been rendered moot. The rejection as it is applied to claims 2-7, 20-27, 29-37, 47, 49, 51, 52, 55, 56, 70-73, 76-78, 81-83, 105-110, 113-126, 129-135, 137-143, 145-154, 177-181 is respectfully traversed.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1970). Disclosure of a prior art genus that encompasses a claimed species is not sufficient by itself to establish that selection of the species is *prima facie* obvious. *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994). If the cited prior art reference teaches a genus that contains a claimed species without suggesting the species, the genus fails to render the species obvious. *In re Bell* 991 F.2d 781 (Fed. Cir. 1993).

Claims 2, 20, 29, 32, 35, 47, 49, 116, 131, 139, 147, and 154 are the independent claims of the rejected claim set. Each claim recites nucleic acid complexes that are rod-shaped when visualized by transmission electron microscopy.

Hanson is cited as teaching "a compacted and spherical condensed polylysine/DNA complex comprising a single nucleic acid with a diameter of less than 23 nm and further comprising an ion of acetate[1], wherein the charge ratio is of about 1:1, and wherein the polylysine has not been modified at its N-terminal to incorporate a cysteine residue." (Paper 12, page 4, lines 3-5, emphasis added.) Park and Schacht are cited as teaching "the concept of utilizing a polycationic polylysine (PLL) linked to PEG." (Paper 12, page 5,

[1] The pending claims recite nucleic acid complexes that are formed by mixing a nucleic acid molecule and polycation molecules. Prior to mixing, the polycation molecules have acetate as a counterion. The claims do not require that acetate be present in the nucleic acid complexes. Hanson does not teach or suggest such use of acetate.

lines 2-3.) Park is also cited as teaching that "PEG of MW 0.5-20 K MW linked to PLL even further enhances the delivery of a charged therapeutic agent across the bilayer membrane of a target cell." (Paper 12, page 5, lines 8-9.) The Office Action states that one of ordinary skill in the art would have been motivated to modify Hanson's teaching of a polylysine with Park's and Schacht's teachings of linking PEG to a polycation because Park and Schacht teach that "PEG linked to PLL even further enhances the delivery of a charged therapeutic agent across the bilayer membrane of a target cell." (Paper 12, page 5, lines 18-19.)

The Office Action further cites Schacht as teaching that a disulfide bond can be used to link PEG to a molecule. (Paper 12, page 5, lines 21-22.) The Office Action asserts:

> It would have been obvious for one of ordinary skill in the art to have further modified the N-terminal of the polylysine by providing a disulfide bridge so as to act as [a] bridge for PEG's linkage. One of ordinary skill in the art would have been motivated to employ a cysteine, which is well-known in the art as a source of a disulfide bond used as an attachment point or a reactive group because such use of any reactive group including the use of a disulfide bond from any source is also taught in the Schacht reference.

Paper 12, page 5, line 23 to page 6, line 2.

Serres and Lollo are additionally cited for teaching polycationic polymers having counterions such as chloride and the use of salts and counterions to enhance the compaction of DNA without aggregation of carrier molecules. (Paper 12, page 6, lines 3-9.)

None of the cited references teaches or suggests unaggregated nucleic acid complexes that "are rod-shaped when visualized by transmission electron microscopy." Hanson, as discussed above, teaches nucleic acid complexes that contain a nucleic acid and a nucleic acid-binding carrier. (Column 19, lines 50-52.) The complexes are spherical or

toroid-shaped. Hanson teaches, "Condensed DNA is in a state in which interaction with the solvent is minimal and therefore the DNA is in the form of isolated spheres or toroids." (Column 19, lines 60-62.) Hanson does not suggest that his condensed DNA complexes have any shape other than that of a sphere or a toroid. In fact, Hanson teaches away from the DNA complexes having a shape other than the shape of a toroid. Hanson teaches, if "DNA is **properly** condensed; only individual toroids can be seen." (Column 6, lines 8-9, emphasis added.)

Park does not teach or suggest DNA complexes that "are rod-shaped when visualized by transmission electron microscopy" and thus fails to remedy the deficiency of Hanson. Park teaches polylysine peptide conjugates that are in a complex with nucleic acids. Park does not teach or suggest the shape of the polylysine conjugate-nucleic acid complexes. Thus Park cannot teach or suggest nucleic acid complexes that "are rod-shaped when visualized by transmission electron microscopy."

Schact also does not teach or suggest DNA complexes that "are rod-shaped when visualized by transmission electron microscopy" and thus does not remedy the deficiency of Hanson. Schact teaches nucleic acid carrier complexes containing nucleic acid molecules and a cationic polymer, *e.g.*, polylysine. Schact teaches that the nucleic acid carrier complexes are spherical. Schact teaches that "the complexes will generally have a compact and roughly spherical core composed of condensed DNA and the cationic polymer material." (Page 47, lines 1-2.) Thus Schact does not teach or suggest nucleic acid complexes that are rod-shaped.

Serres also does not teach or suggest DNA complexes that "are rod-shaped when visualized by transmission electron microscopy" and thus does not remedy the deficiency of

Hanson. Serres teaches condensation of DNA in complexes using polynorbornane polycation polymer. Serres teaches that DNA condensed with polynorbornane polycation polymers is spherical or toroid-shaped when visualized by transmission electron microscopy. Serres teaches, "In some cases DNA appeared to be compacted into relatively dense particles with toroidal (Figure 3A) and spheroidal (Figure 3B) morphologies frequently observed for DNA and small multivalent cations." (Page 6959, column 1, lines 6-10; See also Figure 1.) Serres does not suggest that the DNA complexes have or should have any other shape. Thus Serres does not teach or suggest DNA complexes which are rod-shaped when viewed by transmission electron microscopy.

Lollo also does not teach or suggest DNA complexes that "are rod-shaped when visualized by transmission electron microscopy" and thus does not remedy the deficiency of Hanson. Lollo teaches that cationic moieties are used as carrier molecules to bind polynucleotides to form polynucleotide carrier complexes. Lollo does not teach the shape of the polynucleotide carrier complexes produced by his method. However, Lollo does teach the shape of complexed nucleic acids produced by others. Lollo teaches that prior art nucleic acid complexes had a toroidal shape. Lollo teaches, "Wagner et al. recognized that the polycation not only served to link the DNA, but also functioned to condense the DNA into small toroid structures of approximately 80-100 nanometers in diameter, facilitating its uptake by cells." (Page 2, lines 14-17.) Lollo also teaches the prior formation of non-functional nucleic acid compositions, some of which had the shape of rods: "The authors [Perales *et al.*[2]] observed that when increasing the ionic strength of the mixture above the critical salt concentration, the DNA complexes assumed a non-functional rod-like

[2] The non-functional rods described in Lollo are taught in Perales *et al.*, *Proc. Natl. Acad. Sci.* (1994) *91*: 4086-4090; see page 4088 of Perales at column 2, lines 4-7 (Exhibit A).

conformation of increased diameter." (Page 2, lines 32-34.) This observation is also described in the Hanson patent 5,844,107: "In Fig. 1F, we see a DNA complex, at a concentration of 1.068M NaCl, which is above optimal for condensation of this complex. The DNA is in the relaxed state. Note the branched unimolecular toroids in which a nucleus of condensation is visible and the rod-like DNA fibers." (Column 6, lines 11-16.) Hanson teaches that the non-functional rod-like complexes contain DNA in a relaxed state. The DNA is visualized as partially condensed toroids and unraveled, rod-like fibers. Thus, the rod-like compositions to which Lollo refers are DNA fibers, not complexes of DNA and polycation.

Thus the combination of Hanson, Park, Schadt, Serres, and Lollo fails to teach or suggest the nucleic acid complexes recited in claims 2, 20, 29, 32, 35, 47, 49, 116, 131, 139, 147, and 154. Claims 3-7, 21-27, 30, 31, 33, 34, 36, 37, 51, 52, 55, 56, 70-73, 76-78, 81-83, 105-110, 113-115, 117-126, 129, 130, 132-135, 137, 138, 140-143, 145, 146, 148-153, and 177-181 depend from these claims and thus also contain the recitation of nucleic acid complexes that "are rod-shaped when visualized by transmission electron microscopy." The *prima facie* case of obviousness must fail. Withdrawal of this rejection to claims 2-7, 20-27, 29-37, 47, 49, 51, 52, 55, 56, 70-73, 76-78, 81-83, 105-110, 113-126, 129-135, 137-143, 145-154, and 177-181 is respectfully requested.

Furthermore, dependent claims 4, 22, 31, 34, 37, 52, 54, 56, 58, 105-110, 118-126, 127, 129, 130, 132-135, 137, 138, 140-143, 145-153, and 177-181 recite that the polycation molecule of the nucleic acid complexes is a polylysine peptide with a cysteine residue or is a particular polylysine peptide with a cysteine residue. None of the cited references teaches or suggests a polylysine peptide with a cysteine residue as recited in these dependent

claims. Hanson teaches polycations that form complexes with DNA. Hanson teaches, "A preferred polycation is polylysine. Other potential nucleic acid binding moieties include Arg-Lys mixed polymers, polyarginine, polyornithine, histones, avidin, and protamines." (Column 16, lines 15-18.)

Park teaches polylysine peptide conjugates that are in a complex with nucleic acids. The polylysine peptides contain "a polylysine (PLL) member covalently bound to a polyethylene glycol member (PEG-PLL), which in turn [is] covalently bound to a targeting moiety (TM), recognizable by cell membrane receptors." (Column 5, lines 11-15.)

Schacht teaches nucleic acid carrier complexes containing nucleic acid molecules and a cationic polymer, *e.g.*, polylysine. Schacht teaches, "In some embodiments one presently favoured cationic polymer is poly(L)lysine (pLL), preferably with a molecular weight (weight average) greater than 3 kDa but below 25 kDa, and most preferably in the range 4-20 kDa, in order to provide complexes of a suitable size. However, other polyamino acids, e.g. poly(L)orithine, can also be suitable, and in some other embodiments non-polypeptide synthetic polymers may be used." (Page 10, lines 9-17.)

Serres teaches condensation of DNA in complexes using polynorbornane polycation polymer. Serres also teaches that DNA can be condensed using "linear cationic polymers such as polylysine derivatives or branched polymers such as polyamidoamines, polyethylenimine 'Proton Sponge.'" (Page 6956, column 1, lines 16-18, citations omitted.)

Lollo teaches that cationic moieties are used as carrier molecules to bind polynucleotides to form polynucleotide carrier complexes. Lollo teaches, "Preferred cationic moieties for use in the carrier are polycations, such as polylysine (e.g., poly-L-lysine), polyarginine, polyornithine, spermine, basic proteins such as histones, avidin,

protamines, modified albumin (i.e., N-acylurea albumin) and polyamidoamine cascade polymers. A preferred polycation is polylysine (e.g., ranging from 3,800 to 60,000 daltons)." (Page 9, lines 18-24.)

Thus Hanson, Schacht, Park, Serres, and Lollo teach nucleic acid complexes that contain polylysine peptides. The combination of references also teaches that the polylysine peptides can be modified to contain other amino acids. The other amino acids are arginine and ornithine. None of Hanson, Schacht, Park, Serres, or Lollo teaches the use of a cysteine on a polylysine peptide.

The Office Action asserts, however, that the cited references suggest adding a cysteine residue to the polylysine peptide taught by Hanson because Schacht teaches that a disulfide bond can be used to link PEG to a molecule and cysteine moieties are known to contain a thiol group. (Paper 12, page 5, line 21 to page 6, line 2.) As discussed above, none of the cited references suggests addition of a cysteine residue to a polylysine peptide. In addition, while Schacht teaches that a disulfide bond can link PEG to a molecule, none of Hanson, Schacht, Park, Serres, or Lollo provides any suggestion that of the genus of molecules that contain thiol groups, a cysteine residue should be selected as the molecule that contains the thiol. This suggestion is found in the applicants' specification but appears not to be in the prior art. The suggestion for combining references cannot, however, be taken from the specification. *In re Gorman* 933 F.2d 982, 987 (Fed. Cir. 1992).

Hanson teaches that molecules can be attached to polylysine peptides via modification of the polylysine peptide with a thiol group. Example 3 of Hanson teaches attachment of a Fab fragment to a polylysine peptide using a thiol group provided by N-succinimidyl 3-(2-pyridyldithio) proprionate (SPDP): "The Fab fragment of the anti-pIgR

immunoglobulin G was covalently linked to poly (L-lysine) (Mr 10,000 Da) using the heterobifunctional crosslinking reagent N-succinimidyl 3-(2-pyridyldithio) proprionate (SPDP)." (Column 38, lines 5-9.) Thus Hanson provides no teaching that would suggest selecting the amino acid residue cysteine from the genus of molecules containing thiol groups to attach to a polylysine peptide.

Schacht teaches that a thiol is used to attach PEG to a polycation. Schacht teaches, "In general, the reactive groups on the polycation . . . for forming the linkages may be selected from thiol . . . groups." (Page 11, lines 26-27.) Schacht points to SPDP and *m*-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) as a source of thiol groups that are attached to the polycation. Schacht teaches, "The polyamine (poly-L-lysine, polyallylamine, polyethyleneimine, etc.) is partially modified to introduce side chains with reactive terminal groups by reacting with N-succinimidyl 3-(2-pyridyldithio)propionate (SPDP) and is then mixed with DNA giving a polyelectrolyte complex. The addition of α-methoxy-ω-thiol-polyethyleneoxide (pEG-SH) then leads to grafting of hydrophilic pEG blocks onto the polyamino backbone via labile S-S bonds." (Page 25, lines 28-33.) Schacht also teaches, "In this Example, poly(L)lysine is partially modified with *m*-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) and the reaction product is then reacted with a fusogenic peptide having a reactive thiol group . . . " (Page 48, lines 12-14.) Thus Shacht does not point to or provide any teaching that would suggest to one of skill in the art that a cysteine residue be the source of the thiol group.

Park teaches nucleic acid complexes that contain a molecule that contains polylysine, PEG, and a targeting moiety: "This invention relates to a composition capable of forming stable, soluble complexes with nucleic acids and the method of preparation

thereof comprising a polylysine (PLL) member covalently bound to a polyethylene glycol member (PEG-PLL), which in turn covalently bound to a targeting moiety (TM), recognizable by cell membrane receptors." (Column 5, lines 9-15.) Park, however, does not teach that the polylysine or targeting moiety is linked to PEG using a thiol group. See column 7, lines 28-58, column 8, lines 18-48, column 8, line 51 to column 9, line 4, column 13, lines 10-62, and column 13, line 65 to column 14, line 44. Thus Park cannot suggest selection of a cysteine residue as a thiol to link a molecule to polylysine.

Serres teaches polynorbornane polycationic polymers that form complexes with nucleic acids. "The DNA/polymer complexes were made up by adding different solutions of polymer to DNA (1 μg of DNA corresponds to 3 nmol of phosphate) solubilized in phosphate buffer pH 7.4." (Page 6957, column 1, lines 45-47.) Serres provides no teaching that polycations are linked to a second molecule and thus does not teach the use of a thiol group, or cysteine, to link a polycation to a second molecule.

Lollo teaches polynucleotide carrier complexes that contain polynucleotides and carrier molecules. The carrier molecules have a portion that binds to the polynucleotide and a portion that recognizes the surface of a target cell. (Page 7, lines 31-36.) Lollo teaches that thiol groups can be used to link the two portions. However, Lollo only suggests that the thiol group is derived from sulfhydryl reagents similar to those suggested by Hanson and Schacht, *e.g.*, SPDP: "Alternative linkages are disulfide bonds which can be formed using cross-linking reagents, such as N-Succinimidyl 3-(2-pyridyldithio)propionate (SPDP), N-hydorxysuccinimidyl ester of chlorambucil, N-Succinimidyl-(4-Iodoacetly)aminoben zoate) (SIAB), Sulfo-SIAB, and Sulfo-Succinimidyl-4-maleimidophenyl-butyrate (Sulfo-SMPB)." (Page 10, lines 4-8.) Thus Lollo also

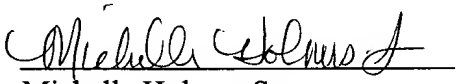
provides no teaching that suggests selecting the amino acid residue cysteine from the genus of molecules containing thiol groups to attach to a polylysine peptide.

The combination of Hansen, Schacht, Park, Serres, and Lollo does not teach or suggest "polylysine peptides with a cysteine residue" as recited in the rejected claims. Thus the combination of Hansen, Schacht, Park, Serres, and Lollo is not sufficient to render claims 4, 22, 31, 34, 37, 52, 56, 105-110, 118-126, 127, 129, 130, 132-135, 137, 138, 140-143, 145-153, and 177-181 *prima facie* obvious.

The rejection of claims 4, 22, 31, 34, 37, 52, 56, 105-110, 118-126, 127, 129, 130, 132-135, 137, 138, 140-143, 145-153, and 177-181 should be withdrawn.

Respectfully submitted,

Date: April 28, 2003

By: 
Michelle Holmes-Son
Reg. No. 47,660

BANNER & WITCOFF, LTD
1001 G Street, N.W.
Eleventh Floor
Washington, D.C. 20001-4597
(202) 508-9100